Remarks

Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-14 are currently pending in the application. Claims 2, 9, 10, 12, 13, 21, 22, 24-48, 59 and 65-93 have been withdrawn from consideration due to the Examiner's previous restriction requirement. Claims 3, 11, 15, 23, 50, 58, 94-97, 99, 105 and 106 have been canceled in a previous reply. Claim 1 is presently amended and support for the amendment is found throughout the present application, e.g., at page 15, line 23 through page 17, line 17 and the claims as-filed.. These claims have been amended, withdrawn or canceled without prejudice to, or disclaimer of, the subject matter thereof. Applicants reserve the right to file divisional and continuing applications directed to the subject matter of any claim withdrawn or cancelled for any reason.

By these remarks and amendments, Applicants do not acquiesce to the propriety of any of the Examiner's prior rejections and do not disclaim any subject matter to which Applicants are entitled. *Cf. Warner Jenkinson Co. v. Hilton-Davis Chem. Co.*, 41 U.S.P.Q.2d 1865 (U.S. 1997).

Claim Rejections under 35 U.S.C. § 103

The Examiner has sustained the rejection of Claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 under 35 U.S.C. § 103 as obvious over United States Patent Number 5,547,979 ("Christensen") in view of the Merck Manual. OA at 3. According to the Examiner, Christensen teaches "the phosphodiesterase inhibitor[] rolipram . . . in a method of treating stroke in a human." *Id.* The Examiner also notes that: "The active ingredient may be administered from 1 to 6 times a day or as recognized by one of ordinary skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the condition, the form, route, site of administration, patient, and that such optimums can be determined by conventional techniques." *Id.* The Examiner further states that: "the limitations regarding 'which enhances CREB pathway function' and 'wherein rehabilitation of said cognitive deficit is effect by producing a long lasting performance gain' are given little patentable weight because these biological processes are inherent when the same compound is administered in the same patient population at the same dosage." *Id.* at 3-4.

The Examiner concedes that Christensen fails to disclose "multiple cognitive training sessions sufficient to produce an improvement in performance of a cognitive

task whose deficit is associated with a central nervous system disorder." OA at 4. However, the Examiner posits that this failing of Christensen is remedied by the Merck Manual. According to the Examiner, the Merck Manual teaches that "a training protocol should be started as early as possible towards a patient's rehabilitation to stroke. Such rehabilitation includes encouragement, orientation toward the outside environment, eating, dressing, toilet functions, other basic needs, passive exercise, particularly of paralyzed limbs, and breathing exercises." *Id.* The Examiner concludes that these rehabilitation techniques meet the limitation of cognitive training and also notes that "it is obvious to one of ordinary skill in the art to not stop at a single training session in the rehabilitation of a stroke victim since the process takes a great deal of time with many repeated sessions." *Id.*

The Examiner continues that a person of ordinary skill in the art would have two reasons to combine the cited references: "(1) both Christensen and the Merck Manual disclose treatment for the same purpose, which is treating stroke patients and because (2) of the additive therapeutic effects of employing two methods of treating stroke simultaneously." OA at 5. The Examiner concludes that it would have been obvious "to have combined the cognitive multiple training sessions, as described in the Merck Manual, before and during administration of the phosphodiesterase inhibitor, rolipram, in the method of treating stroke in a human, as disclosed by Christensen." *Id.* Applicants respectfully traverse.

To maintain a proper rejection under 35 U.S.C. § 103, the Examiner must meet four conditions to establish a *prima facie* case of obviousness. First, the Examiner must show that the prior art suggested to those of ordinary skill in the art that they should make the claimed composition or device or carry out the claimed process. Second, the Examiner must show that the prior art would have provided one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be adequately founded in the prior art and not in an applicant's disclosure. Third, the prior art must teach or suggest all the claim limitations. *In re Vaeck,* 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Fourth, if an obviousness rejection is based on some combination of prior art references, the Examiner must show a suggestion, teaching, or motivation to combine the prior art references ("the TSM test"). *In re Dembiczak,* 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). Following *KSR Int'l Co. v. Teleflex, Inc.*, this fourth prong of the *prima facie*

obviousness analysis must not be applied in a rigid or formulaic way such that it becomes inconsistent with the more flexible approach of *Graham v. John Deere*, 383 U.S. 1, 17-18 (1966). 127 S. Ct. 1727 (2007). It must still be applied, however, as the TSM test captures the important insight that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *Id.* citing *United States v. Adams*, 383 U.S. 39, 50-52 (1966).

Christensen does not teach or suggest the improvement in performance of a cognitive task following application of PDE4 inhibitors to treat stroke, as contended by the Examiner. Instead, Christensen relates to PDE4 inhibitors, such as rolipram, that inhibit the production of Tumor Necrosis Factor (TNF), which "has pro-inflammatory activities which together with its *early* production (during the *initial* stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock." Col. 6, ll. 20-25 (emphasis added). The only proper interpretation of this statement is that PDE4 inhibitors may inhibit the inflammatory response, thereby preventing further tissue damage often associated with inflammation during the immediate time period following a brain injury. Indeed, this portion of Christensen effectively teaches away from the repeated application of PDE4 inhibitors in conjunction with stroke, due to the *early* production of TNF during the *initial* stage of an inflammatory event.

Applicants established in their prior response that Christensen relates to the treating various "disease states mediated or exacerbated by TNF production." Christensen, Abstract. Indeed, Christensen's methods all focus on the administration of a "TNF inhibiting amount" of a compound. *See, e.g., id.* Col 2, ll. 10-20. Christensen therefore only relates to the use of the compounds for mediation of TNF exacerbated tissue injury (for example, after stroke) and does not teach or suggest the improvement in performance of a cognitive task following application of PDE4 inhibitors, much less the repeated application of PDE4 inhibitors in conjunction with repeated cognitive training to produce a long-lasting performance gain, as claimed. The present rejection is exactly the same as the situation as admonished by the Supreme Court in *Graham*, where "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." 383

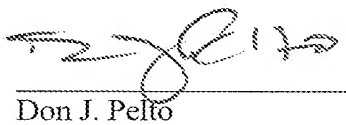
U.S. 1, 17-18 (1966). 127 S. Ct. 1727 (2007). Christensen merely relates to use of rolipram for mediation of tissue injury exacerbated by TNF. The Merck Manual merely relates to the physical rehabilitation of stroke patients. Indeed, there nothing of record that the physical rehabilitation of stroke patients, as independently set forth in the Merck Manual, should be combined with Christensen's independent use of rolipram for mediation of tissue injury exacerbated by TNF,

Indeed, neither Christensen nor the Merck Manual, alone or in combination, teach or suggest the improvement in performance of a cognitive task following application of PDE4 inhibitors, much less the repeated application of PDE4 inhibitors in conjunction with repeated cognitive training to produce a long-lasting performance gain relative to training alone, as claimed. – these elements are individually and collectively absent from the prior art of record and the present rejection can only be a case of improper hindsight reasoning. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections of claims 1, 4-8, 14, 16-20, 49, 51-57, 60-64, 98 and 100-104 stand rejected under 35 U.S.C. § 103 as obvious over Christensen in view of the Merck Manual.

CONCLUSION

Applicants have properly and fully addressed each of the Examiner's grounds for rejection. Applicants submit that the present application is now in condition for allowance. If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account

Respectfully submitted,



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